Original Article

Gender Disparity in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndromes – Does it Still Exist in Contemporary Practice?

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Abstract

Introduction: Prior studies have demonstrated evidence of a disparity in the treatment and outcome of male compared to female patients undergoing percutaneous coronary intervention (PCI). Materials and Methods: From a dedicated database, we retrospectively analysed all consecutive patients with acute coronary syndrome (ACS) admitted to our institution for PCI in 2008. Baseline and procedural characteristics as well as complications were then evaluated for male patients (n = 331) as compared with female patients (n = 137). Results: Women were noted to be older at the time of presentation (66.1 ± 10.0 vs 60.7 ± 11.6 years, *P* <0.00001), the groups were otherwise well matched in terms of baseline characteristics. Female patients were treated with significantly smaller diameter stents (2.86 ± 0.44 vs 2.96 ± 0.50 mm, *P* = 0.04), though the proportion of drug-eluting stents was similar (53.7% vs 50.5%, *P* = 0.5). Female patients were significantly less likely to receive optimal medical therapy with lesser use of glycoprotein IIb/IIIa inhibitor (26.3% vs 55.3%, *P* <0.0000001), and beta-blockers (83.9% vs 90.9%, *P* = 0.04). At 30 days, there were no differences in the rate of major adverse cerebrovascular or cardiac events (2.9% vs 3.9%, *P* = 0.8), though females had a significantly higher rate of femoral access site pseudoaneurysm (4.4% vs 0.9%, *P* = 0.02). Conclusions: There remains evidence for continued gender disparity in contemporary practice; despite evidence for efficacy in ACS patients, females received a notably lower use of glycoprotein IIb/IIIa inhibitors and beta-blockers. Women are also significantly more likely to develop femoral access site complications with pseudoaneurysm development; it is important therefore to optimise procedures for sheath removal in female patients or give strong consideration to the use of radial access site.

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Introduction

Globally, cardiovascular disease (CVD) is the single most common cause of death among women; and in parallel with an increasing life expectancy, the proportion of women who have CVD is also rising. Registry data demonstrate that women tend to be 10 years older than men at the time of presentation with CVD. Invasive investigation and subsequent revascularisation have been established as beneficial in reducing fatal and non-fatal ischaemic complications in patients with acute myocardial infarction (AMI) and high-risk acute coronary syndromes (ACS).[1] However, numerous large registries have demonstrated that there is a gender disparity in this treatment, with women significantly less likely to undergo revascularisation than their male counterparts.[2-6] The precise reasons for this are unclear, though are likely to be multifactorial. At presentation, women with ACSs tend to be older and have a higher prevalence of comorbidities and risk factors such as hypertension, diabetes, and hypercholesterolemia.[7] Furthermore, women tend to have smaller coronary vessels and may have been deemed less suitable to undergo revascularisation particularly with percutaneous coronary intervention (PCI). Recent data have, however, demonstrated the efficacy of drug-eluting stents in women and may help to broaden the applicability of PCI to female patients.[8,9]

The aim of the present study was to evaluate the practice

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of our tertiary referral centre in the UK to see whether there is evidence of continued gender disparity in contemporary practice with the availability of drug-eluting stents.

Materials and Methods

From a dedicated database, we identified all consecutive patients with ACS who underwent PCI at our institution in 2008. During this period, patients admitted with acute ST-elevation myocardial infarction (STEMI) during working hours underwent primary PCI, those admitted outside these hours were treated with thrombolysis as the default strategy, with rescue PCI undertaken if reperfusion did not occur within 90 minutes (based on <50% resolution of ST segments on the ECG). The decision to undertake invasive investigation in patients with ACS was at the discretion of the treating physician. The study aimed to focus on the evidence of gender disparity in the treatment of patients with ACS during the 12 months period of 2008.

Interventional Procedures

Following diagnostic coronary angiography, percutaneous revascularisation was undertaken at the discretion of the treating cardiologist. Wherever possible (patients without on-going symptoms at rest and without haemodynamic instability), those with multi-vessel/complex disease were first discussed at a multi-disciplinary team meeting comprising general cardiologists, interventional cardiologists, and cardiothoracic surgeons, to determine a consensus view on the most appropriate therapeutic strategy. All interventions were performed according to standard techniques, with the final PCI strategy left at the discretion of the operator. Choice of stent type [drug-eluting (DES) or bare metal (BMS)] was governed by guidance from the National Institute of Clinical Excellence (NICE) in the UK. This states that BMS should be used in preference to DES for short lesions (<15 mm) that occur in large vessels (>3 mm diameter). In addition, BMS are preferred in lesions with angiographic evidence of thrombus. Unless contra-indicated, all patients were given a pre-load of aspirin 300 mg and clopidogrel 600 mg prior to the procedure. They were subsequently recommended to take both aspirin and clopidogrel 75 mg od for a duration of 12 months, irrespective of stent type. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator.

Statistical Analysis

Continuous variables were summarised as mean ± standard deviation and compared with Student's *t*-test. Categorical variables are presented as counts and percentages and compared with Fisher's Exact test or chi-square test. All statistical tests were two-tailed. A P value <0.05 was considered significant. All statistical analysis was performed using SPSS version 16 (SPSS, Inc. Chicago, Illinois).

Results

Of a total of 468 consecutive patients who underwent PCI for ACS, 137 (29.3%) were female. The baseline demographic data with respect to gender are presented in Table 1. Female patients were notably older than the male counterparts but no other significant differences in the baseline characteristics were detected. The majority of patients in both groups were treated for non-ST-elevation acute myocardial infarction (NSTEMI) with only 91(19.4%) treated for STEMI.

Procedural data are presented in Table 2. There was no significant difference in the extent of disease or lesion location; however, female patients were treated with a significantly lower rate of glycoprotein IIb/IIIa inhibitor use. The number and type of stent utilised (drug-eluting vs bare metal) were not significantly different; however, the stents used in female patients were significantly smaller in diameter (2.86 ± 0.44 vs 2.96 ± 0.50 mm, P = 0.04), and the total stent length was shorter.

Table 3 depicts the cardiac medication prescribed for female compared to male patients and shows a significantly lower use of beta-blockers in the female patients. The vast majority of patients were prescribed aspirin and statin.

The short-term (30 day) adverse clinical events are shown in Table 4. There was a low rate of adverse events, with no

Table 1. Baseline Characteristics with Respect to Gender

	Female n = 137	**Male n = 331**	***P***
Mean age (y)	66.1 ± 10.0	60.7 ± 11.6	<0.00001
Current smoker (%)	50 (36.5%)	114 (34.4%)	0.7
Hypertension	80 (58.4%)	169 (51.1%)	0.2
Diabetes	14 (10.2%)	47 (14.2%)	0.3
Insulin	4 (2.9%)	16 (4.8%)	0.5
Family history	69 (50.4%)	155 (46.8%)	0.5
Hypercholesterolaemia	120 (87.6%)	293 (88.5%)	0.8
Cerebrovascular disease	6 (4.3%)	13 (3.9%)	0.8
Chronic pulmonary disease	17 (12.4%)	41 (12.4%)	1.0
Previous myocardial infarction	22 (16.1%)	65 (19.6%)	0.4
Previous PCI	16 (11.7%)	40 (12.1%)	1.0
Previous CABG	3 (2.2%)	12 (3.6%)	0.6
Presentation			0.9
STEMI (primary PCI)	11 (8.0%)	36 (10.9%)	
(rescue PCI)	11 (8.0%)	33 (10.0%)	
NSTEMI	115 (83.9%)	262 (79.2%)	

CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention; NSTEMI: non-ST-elevation acute myocardial infarction

Table 2. Procedural Characteristics

	Female n = 137	Male n = 331	*P*
Access route			0.3
Femoral (%)	113 (82.5%)	259 (78.2%)	
Radial (%)	24 (17.5%)	72 (21.8%)	
Extent of disease			0.3
Single vessel	67 (48.9%)	136 (41.1%)	
2 vessel	53 (38.7%)	120 (36.3%)	
3 vessel	17 (12.4%)	75 (22.7%)	
Use of GP IIb/IIIa inhibitor (%)	36 (26.3%)	183 (55.3%)	<0.0000001
Thrombus evidence on angiography	33 (16.5%)	110 (22.1%)	0.1
Mean number of lesions treated	1.46 ± 0.73	1.50 ± 0.83	0.6
De novo	188 (94.0%)	473 (95.2%)	
In-stent restenosis	12 (6.0%)	24 (4.8%)	
Site of lesion			0.8
LMS	2 (1.0%)	9 (1.8%)	
LAD	84 (42.0%)	208 (41.9%)	
LCx	40 (20.0%)	107 (21.5%)	
RCA	72 (36.0%)	163 (32.8%)	
SVG	2 (1.0%)	10 (2.0%)	
Mean number of stents implanted per patient	1.37 ± 0.65	1.44 ± 0.87	0.4
Proportion of DES used (%)	53.7%	50.5%	0.5
Mean diameter of stent used (mm)	2.86 ± 0.44	2.96 ± 0.50	0.04
Mean total length of stent(s) used per lesion (mm)	20.23 ± 9.52	22.68 ± 13.3	0.03
Final TIMI III flow in culprit lesion	95.6%	97.9%	0.2
Mean number of days in hospital	6.36 ± 8.43	5.73 ± 7.21	0.4

LAD: left anterior descending; LCx: left circumflex; LMS: left main stem; RCA: right coronary artery; SVG: saphenous vein graft

Table 3. In-hospital Cardiac Medications

	Female (n = 137)	Male (n = 331)	*P*
Aspirin	133 (97.1%)	327 (98.8%)	0.2
Statin	131 (95.6%)	318 (96.1%)	0.8
Beta blocker	115 (83.9%)	301 (90.9%)	0.04
ACE inhibitor	98 (71.5%)	257 (77.6%)	0.2

Table 4. Adverse Clinical Events Within 30 Days

	Female (n = 137)	Male (n = 331)	*P*
Cardiogenic shock	7 (5.1%)	12 (3.6%)	0.5
Death	3 (2.2%)	8 (2.4%)	1.0
Stroke	1 (0.7%)	3 (0.9%)	1.0
Myocardial infarction	1 (0.7%)	5 (1.5%)	1.0
TLR PCI CABG	0	2 (0.6%) 1 (0.3%) 1 (0.3%)	1.0
MACCE – free of death/ AMI/CVA/TLR	4 (2.9%)	13 (3.9%)	0.8
Femoral access site complication False aneurysm	7 of 113 (6.2%)	4 of 259 (1.5%)	0.02
Significant haemorrhage	2 (1.5%)	5 (1.5%)	1.0

AMI: acute myocardial infarction; CABG: coronary artery bypass graft surgery; CVA: cerebrovascular accident; MACCE: major adverse cerebrovascular and cardiac events; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation

significant difference in the overall rate of major adverse cerebrovascular and cardiac events (MACCE) between female and male patients (2.9% vs 3.9%, $P = 0.8$). Female patients were at increased risk of suffering a femoral access site complication with pseudoaneurysm development (6.2% vs 1.5%, $P = 0.02$). Further analysis demonstrated that of those patients treated from a femoral route, Angioseal was used in 50 (44.2%) females compared to 141 (49.4%) males ($P = 0.4$). Of the 13 patients who suffered a pseudoaneurysm, only 2 had been treated with an Angioseal and none had received glycoprotein IIb/IIIa inhibitor.

Discussion

The present study evaluated 468 consecutive ACS patients who underwent PCI in our institution in 2008 thereby reflecting contemporary practice at a tertiary referral centre in the UK. The study demonstrated several important differences between female and male patients. Firstly, female patients were significantly older than their male counterparts. Secondly, the stents used in female patients were significantly smaller in diameter. Thirdly, female patients were less likely to be treated with optimal medical therapy, with lesser use of glycoprotein IIb/IIIa inhibitors and beta-blockers. Furthermore, though there were no significant differences in the short-term adverse event rate at 30 days, female patients had a higher incidence of femoral complication due to false aneurysm.

Female patients accounted for a minority (only 29%) of the cohort treated in this registry of consecutive patients. One of the limitations of the present study is that it does not take into account those ACS patients who were managed medically or with coronary artery bypass graft (CABG) surgery. However, the proportion of female patients is consistent with that of other previously reported multicentre registries;[10-12] for

example, female patients comprised 33% of 31,982 patients with ACS included in the prospective multicentre GRACE registry (Global Registry of Acute Coronary Events).[12] In contrast, females comprised a higher proportion (41%) of the 35,875 patients included in the multicentre CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative.[13] This difference raises the possibility that, in some registries, there may be bias against female patients undergoing cardiac catheterisation.[6,14] Indeed, this was evident in data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial which enrolled 12,562 patients with ACS.[6] The investigators found that females (38% of the cohort) underwent significantly fewer invasive procedures including angiography, angioplasty, and CABG surgery (47.6% vs 60.5%; $P = 0.0001$) compared to men.

A lower rate of revascularisation in women was also evident in data from the National Registry of Myocardial Infarction of more than 2.5 million patients treated between 1990 and 2006 in the USA.[2] However, one of the reasons females may be less likely to undergo revascularisation is that they have a higher risk profile. In a large registry of 21,816 patients treated in Canada, females underwent less revascularisation [relative risk 0.67 (95% CI, 0.65 to 0.71)]; however, once adjusted for different clinical variables, there was no longer evidence of a significant difference [relative risk 0.98, (95% CI, 0.87 to 1.01)] with the conclusion that it is important to take the detail of clinical differences into account.

The difference in age at the time of presentation is a frequent finding in multiple previous registries of patients with ACS and myocardial infarction.[4,10-13] This discrepancy is consistent with the delayed onset of coronary artery disease in women whereby oestrogen is thought to have a cardio-protective effect.[15,16]

Historically, a major concern of several studies has been the relatively lower rate of revascularisation in female patients with ACS.[2-6] This is despite clear evidence demonstrating the efficacy in reducing subsequent adverse events. One hypothesis for this is that female patients have smaller-sized coronary vessels and may therefore be more prone to restenosis particularly if treated with bare metal stents.[17-19] Elezi et al[17] evaluated the vessel size of 2602 patients who were successfully treated with (bare metal) stent implantation. They found that females were significantly less likely to have larger vessel size (defined as >3.2 mm) compared with smaller vessel size (19% vs 26%, $P = 0.002$). The current study seems to be in accordance with this as the mean diameter of stent used was significantly smaller in female patients. However, in contemporary practice, females may be more likely to be offered revascularisation with PCI as restenosis has been significantly reduced by the introduction of drug-eluting stents.[20] It is important that female patients included in the present study were not disadvantaged by stent type, and were just as likely as their male counterparts to receive a DES. Though guided by recommendations made by the NICE, ultimately, the choice of stent was at the operator‘s discretion. Female patients are often under-represented in many of the major landmark studies that have evaluated the efficacy of DES; however, there is no evidence to suggest that females derive less benefit from DES. Analysis of patients included in the TAXUS I, II, IV, V and ATLAS studies shows, at 5 years, that women treated with TAXUS stents had a 46% reduction in target lesion revascularisation (TLR) compared with those treated with bare metal stents (12.0% vs 22.2%, $P < 0.001$).[8] Similarly, the analysis of the ARTS II study of 607 patients (23% female), with multi-vessel disease treated with sirolimus-eluting stents, demonstrated no significant difference in the rate of major adverse events at 3 years [19.8% in men vs 17.6% in women, relative risk 1.12 (95% CI, 0.75-1.68), $P = 0.63$].[9]

The major concern of the present study is that in contemporary practice, there appeared to be continued evidence for less optimal medical therapy. In particular, females were less likely to receive treatment with beta-blockers. This is despite no significant difference in the rate of significant chronic obstructive lung disease which might be considered to be a relative contraindication to beta blockade therapy and we therefore cannot explain a possible reason for this. It is, however, in accordance with a study of more than 74,000 patients hospitalised in France with an AMI.[4] Women (30%) were less likely to receive early medical treatments (aspirin and beta-blockers), acute reperfusion therapies and invasive procedures. Subsequently, women had a significantly higher rate of hospital mortality (14.8% vs 6.1% in men, $P < 0.0001$), and though they tend to be older, the increase in mortality remained evident even after adjustment for age. There was no difference in early MACCE evident in our study between males and females; however, this may simply reflect the smaller size of our registry, and the importance of optimal therapy to improve prognosis should not be undermined.

In our study, female patients were also significantly less likely to be treated with a glycoprotein IIb/IIIa inhibitor. This powerful antiplatelet therapy has been shown to be effective in patients with ACS in reducing the rate of adverse cardiac events (death, myocardial infarction, urgent revascularisation).[21-27] Studies have suggested intergender differences in platelet response and reactivity, including a

greater sensitivity of the platelets of women to aggregating stimuli,[28-31] thereby raising the possibility that women may derive even more benefits than men from glycoprotein IIb/IIIa inhibitor therapy. In the present study, we observe that this difference in medical therapy did not translate into a difference in short-term clinical outcome; however, the study population size is not sufficiently large enough to evaluate this.

Lower use of glycoprotein IIb/IIIa inhibitors in women was previously seen in other large registries.[5,13] One of the reasons for this is likely to be physicians' fears over an increased risk of bleeding complications in women, especially as females tend to be older and may be of relatively low weight, both risk factors for higher bleeding. In light of these results a prospective study is needed to evaluate, on an individual patient basis, the reasons for not prescribing glycoprotein IIb/IIIa inhibitors. Bleeding occurs particularly when a femoral access site is used; in the present study, there was no significant difference in the rate of radial versus femoral access between men and women, with radial access being used in the minority (20%). Previous studies have shown that the use of a radial access route is associated with fewer bleeding complications[32] and in addition reduces the rate of femoral access site complications. Studies have demonstrated that being female is an independent risk factor for the occurrence of femoral complications particularly false aneurysm.[33,34] It is therefore of concern that the incidence of false aneurysm in our study was particularly high and occurred in 6.2% of those females treated from a femoral route. Further evaluation demonstrated no association of pseudoaneurysm with the use of either a closure device (Angioseal) or a glycoprotein IIb/IIIa inhibitor. Though not included in this study, it would be of interest to evaluate whether such a difference is also evident in elective patients. Measures such as smaller sheath size, fluoroscopy of the groin before catheterisation, and increased attention to access management should be routinely considered in women to decrease complications when a femoral route is utilised. Our rate of false aneurysms in females is higher than that in other published studies and this has led to a review of our departmental procedures for femoral sheath management and we have also seen an increased use of access from the radial route.

The results of our study confirm that even in contemporary practice with the availability of modern PCI techniques and DES there remain several disparities in the treatment of male and female patients. These results emphasise the importance of ensuring optimal therapy in female (often high-risk) patients to improve prognosis. Indeed, high-risk patients with multiple comorbidities may be denied access to invasive treatment due to physicians' concerns; however these patients are likely to derive most benefit from a more aggressive strategy. Future studies on ACS patients should try to include a high proportion of female patients to ensure that the study is sufficiently powered to assess the outcomes of females, particularly those at relatively increased risk due to comorbidities. Further studies are particularly needed to determine ways of reducing the femoral access complication rate seen in women.

Limitations

Our study does not take into account potential differences between male and female patients with ACS in the initial referral for diagnostic cardiac catheterisation. In addition, data are not included on other patients with ACS who were not treated with PCI (those managed medically or with bypass graft surgery). The study is a retrospective analysis performed on a relatively small number of consecutive patients treated in a single centre in the UK and may not necessarily reflect practice in other countries and institutions.

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